

Therapeutic Class Overview

Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
 - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2020*).
 - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
 - The Drug Addiction Treatment Act (DATA) of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment [CSAT] 2004*).
 - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2020*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) SC injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
 - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, and the FDA shows that the product has been discontinued (*Drugs@FDA.gov 2020*).
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents; Agents for Chemical Dependency

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride (HCl)* tablet	✓
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Subutex (buprenorphine)* sublingual tablet	✓
Vivitrol (naltrexone) intramuscular (IM) injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
buprenorphine/naloxone* sublingual tablets	✓
Suboxone (buprenorphine/naloxone) sublingual film	✓
Zubsolv (buprenorphine/naloxone) sublingual tablets	- †

*Brand name product was discontinued; however, generic formulations are available.

†Generic version not anticipated until 2032.

(*Drugs @FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving opioids increased to more than 42,000 deaths in 2016 (*SAMHSA 2018*).
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths (*SAMHSA 2018, World Health Organization [WHO] 2014*).
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, most states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2019*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after IM or SC administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2020*).
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio), which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
Evzio (naloxone HCl) auto-injector	-
naloxone HCl* injection	✓
Narcan (naloxone HCl) nasal spray	- †

*Brand name product was discontinued; however, generic formulations are available

†Generic product approved by the FDA, but not yet launched

(*Drugs @FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS
Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/naloxone) film	buprenorphine/naloxone sublingual tablets	Suboxone (buprenorphine/naloxone) film	Zubsolv (buprenorphine/naloxone) sublingual tablets
Treatment of opioid dependence			✓		✓	✓
Treatment of opioid dependence and is preferred for induction		✓				
Maintenance treatment of opioid dependence				✓		
Treatment of moderate to severe opioid use disorder*	✓					

*For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2019, buprenorphine/naloxone sublingual tablets 2019, Bunavail 2019, Sublocade 2019, Suboxone film 2019, Zubsolv 2019*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✓	
Treatment of alcohol dependence	✓	✓
Prevention of relapse to opioid dependence following opioid detoxification		✓

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2019*)

Table 5. FDA-Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✓

(*Prescribing information: Lucemyra 2018*)

Table 6. FDA-Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✓		✓
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine		✓	
Diagnosis of suspected or known acute opioid overdosage		✓	
Adjunctive agent to increase blood pressure in the management of septic shock		✓	

(Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid-negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (n = 32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Weiss 2011, Woody et al 2008*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥ 16 mg/day were more likely to continue treatment compared to patients receiving doses < 16 mg/day; however, no significant difference was seen in the percentage of opioid-positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (n = 758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual

tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (Gunderson et al 2015).

- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (Bahji et al 2019, Dalton et al 2019, Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2015, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011). In a 2019 meta-analysis (N = 150,235 patients across 32 cohort studies), overall mortality rates were higher with methadone vs buprenorphine; however, when comparing time in-treatment to time out-of-treatment, methadone significantly reduced mortality vs buprenorphine (Bahji et al 2019). In another meta-analysis that same year (N = 370,611 patients across 30 studies), buprenorphine demonstrated lower all-cause mortality post-medication assisted therapy (MAT) vs methadone or naltrexone. However, all-cause mortality during MAT was lowest with naltrexone, followed by buprenorphine and methadone (Ma et al 2019).
- When low doses of buprenorphine were studied (≤ 8 mg/day), high doses of methadone (≥ 50 mg/day) proved to be more efficacious (Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997).
- In another 2019 meta-analysis (N = 847 overdose events across 4 studies), there was no statistically significant difference for retention in treatment between patients who received buprenorphine/naloxone vs buprenorphine or methadone alone (Dalton et al 2019).
- In a 24-week, Phase 3, double-blind, placebo-controlled, randomized controlled trial (n = 504), the efficacy and safety of multiple SC injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior to placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with negative self-reports for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) (FDA Advisory Committee Briefing Document, Haight et al 2019).
- Extended-release IM naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (n = 570). More induction failures were seen with extended-release IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (Lee et al 2018). A 12-week, randomized, open-label, noninferiority trial (n = 159) similarly found that extended-release IM naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (Tanum et al 2017).
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (Minozzi et al 2011). A small, randomized, open-label study (n = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (Sullivan et al 2019).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (n = 264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (Gorodetzky et al 2017). Similar results were found in another placebo-controlled trial (Fishman et al 2019). Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion (Gowing et al 2016, Gowing et al 2017). It is likely to be less effective than buprenorphine or methadone for opioid detoxification (Meader 2010).

Products for Emergency Treatment of Opioid Overdose

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (Prescribing information: Evzio 2016, Narcan 2017).

- The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio, 8.58; 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescribing naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).
- A retrospective cohort study including 3,085 patients found that of out-of-hospital naloxone administration improved outcomes for approximately 73% of patients with presumed opioid overdose (*Ashburn et al 2020*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, ASAM, CSAT/U.S., SAMHSA, and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications (*Kampman 2015 [update pending Spring 2020], VHA 2015*).
 - Use of tapered doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the WHO and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*Kampman 2015 [update pending Spring 2020], WHO 2014*).
 - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
 - Buprenorphine products have several warnings and precautions, including abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions.

- Concomitant use of buprenorphine with benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).
- The buprenorphine SC injection also has several unique warnings and precautions, including serious harm or death if administered IV (boxed warning); risks associated with treatment of emergent acute pain; and use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2020*).
- Lofexidine has several warnings and precautions, including risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
 - Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
 - The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
 - The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
 - Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
 - Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
 - Monitor patients on naltrexone for the development of depression or suicidality.
 - Warnings unique to extended-release IM naltrexone include injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
 - The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
 - There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
 - Extended-release IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2020*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal (including adverse cardiovascular events).
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	<ul style="list-style-type: none"> • May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment
naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	<ul style="list-style-type: none"> • Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	SC injection	SC	Monthly (minimum 26 days between doses)	<ul style="list-style-type: none"> • Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	<ul style="list-style-type: none"> • Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.
Vivitrol (naltrexone extended-release)	IM injection	IM	Monthly or every 4 weeks	<ul style="list-style-type: none"> • Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv);	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of	<ul style="list-style-type: none"> • These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	generics equivalent to Suboxone tablet)		<p>4.2 mg/0.7 mg based on the control of acute withdrawal symptoms)</p> <p>Suboxone: Single daily dose (except day 1 of induction: titrate in buprenorphine 2 mg to 4 mg increments at approximately 2-hour intervals based on the control of acute symptoms)</p> <p>Sublingual tablet generics (Suboxone): Single daily dose</p> <p>Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2-hour intervals)</p>	

See the current prescribing information for full details

Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
-	16 mg/4 mg	11.4 mg/2.9 mg

*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	<ul style="list-style-type: none"> After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives. 	<ul style="list-style-type: none"> The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	<p>Adults:</p> <ul style="list-style-type: none"> An initial dose may be administered IV. It may be repeated at 2 to 3-minute intervals if the desired degree of counteraction and improvement in 	<ul style="list-style-type: none"> IM or SC administration may be necessary if the IV route is not available. The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate

Data as of February 7, 2020 KS-U/ MG-U/KMR

Page 9 of 14

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			respiratory functions are not obtained. <i>Children:</i> <ul style="list-style-type: none"> The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained. 	intoxication since absorption may be erratic or delayed.
Narcan (naloxone HCl)	Nasal spray	Intranasal	<ul style="list-style-type: none"> A single spray should be administered into 1 nostril. Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives. 	

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) SC injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for moderate-to-severe opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2020*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019, Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.

- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion (*Gowing et al 2016, Gowing et al 2017*). It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release IM naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release IM naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine (*Kampman 2015 [update pending Spring 2020], VHA 2015*).

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approvals of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who

are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015 [update pending Spring 2020]*).

- According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.
- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

REFERENCES

- Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend.* 2017;174:58-64.
- Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict.* 2004;13 Suppl 1:S42-66.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Ed. Arlington, VA: American Psychiatric Association; 2013:541-546.
- American Society of Addiction Medicine. Opioid Addiction 2016 Facts & Figures. <http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf>. Accessed February 7, 2020.
- Ashburn NP, Ryder CW, Angi RM, et al. One-year mortality and associated factors in patients receiving out-of-hospital naloxone for presumed opioid overdose. *Ann Emerg Med.* 2020 Jan 23. pii: S0196-0644(19)31422-2. doi: 10.1016/j.annemergmed.2019.11.022. [Epub ahead of print].
- Bahji A, Cheng B, Gray S, Stuart H. Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. *Acta Psychiatr Scand.* 2019;140(4):313-339. doi: 10.1111/acps.13088
- Bickel WK, Amass L, Crean JP, et al. Buprenorphine dosing every one, two or three days in opioid-dependent patients. *Psychopharmacology (Berl).* 1999;146(2):111-118.
- Bunavail prescribing information. Biodelivery Sciences International, Inc. Raleigh, NC. October 2019.
- Buprenorphine and naloxone tablet prescribing information. Actavis Pharma, Inc. Parsippany, NJ. October 2019.
- Buprenorphine prescribing information. Sun Pharmaceutical Industries, Inc. Cranbury, NJ. May 2019.
- Center for Substance Abuse Treatment; Substance Abuse and Mental Health Services Administration (SAMHSA). Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville (MD): Substance Abuse and Mental Health Services Administration 2004. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK64245/>. Accessed February 7, 2020.
- Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. *MMWR Morb Mortal Wkly Rep.* 2012;61(6):101-105.
- Coffin P. Prevention of lethal opioid overdose in the community. UpToDate Web site. <http://www.uptodate.com>. Updated June 12, 2019. Accessed February 7, 2020.
- Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med.* 2016;165(4):245-252.
- Committee on Substance Use and Prevention (CSUP). Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. *Pediatrics.* 2016 Sep;138(3). <http://pediatrics.aappublications.org/content/138/3/e20161893.long>. Accessed February 7, 2020.
- Dalton K, Butt N. Does the addition of naloxone in buprenorphine/naloxone affect retention in treatment in opioid replacement therapy?: a systematic review and meta-analysis. *J Addict Nurs.* 2019;30(4):254-260. doi: 10.1097/JAN.0000000000000308.
- Daulouède JP, Caer Y, Galland P, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. *J Subst Abuse Treat.* 2010;38(1):83-89.
- Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. *BMC Public Health.* 2014;14:297.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed February 7, 2020.
- Evzio FDA Summary Review. Drugs@FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2017/208411s001SumR.pdf. Accessed February 7, 2020.
- Evzio prescribing information. Kaleo, Inc. Richmond, VA. October 2016.
- Fareed A, Vayalapalli S, Casarella J, et al. Effect of buprenorphine dose on treatment outcome. *J Addict Dis.* 2012;31(1):8-18.
- Farré M, Mas A, Torrens M, et al. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend.* 2002;65:283-290.
- FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. FDA website. Updated September 26, 2017. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications>. Accessed February 7, 2020.
- FDA: Joint Meeting of Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee. Sublocade FDA Briefing Document. October 31, 2017. <https://www.fda.gov/media/108382/download>. Accessed February 7, 2020.

- Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary-care based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med.* 2014;174(12):1947-1954.
- Fishman M, Tirado C, Alam D, et al. Safety and efficacy of lofexidine for medically managed opioid withdrawal: a randomized controlled clinical trial. *J Addict Med.* 2019;13(3):169-176. doi: 10.1097/ADM.0000000000000474.
- Fry A. Alvogen and Reddy's cleared over US rivals to suboxone. Updated July 15, 2019. Available from: <https://generics.pharmaintelligence.informa.com/GB140502/Alvogen-and-Reddys-Cleared-Over-US-Rivals-To-Suboxone?vid=Pharma>. Accessed February 7, 2020.
- Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med.* 2003;349(10):949-958.
- Gibson A, Degenhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long term mortality. *Addiction.* 2008; 103(3):462-468.
- Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol.* 2015;2(1):10.
- Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. *Drug Alcohol Depend.* 2017;176:79-88. doi: 10.1016/j.drugalcdep.2017.02.020.
- Gowing L, Farrell M, Ali R, White JM. Alpha₂-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2016;(5):CD002024. doi: 10.1002/14651858.CD002024.pub5.
- Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2017;2:CD002025. doi: 10.1002/14651858.CD002025.pub5.
- Gunderson EW, Hjelmström P, Sumner M; 006 Study Investigators. Effects of a higher-bioavailability buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone film for the treatment of opioid dependence during induction and stabilization: a multicenter, randomized trial. *Clin Ther.* 2015;37(10):2244-2255.
- Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2019;393(10173):778-790. doi: 10.1016/S0140-6736(18)32259-1.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA.* 1992;267:2750-2755.
- Kakko J, Svanborg KD, Kreek MJ, et al. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet.* 2003;361(9358):662-668.
- Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl.* 2008;10:5-18.
- Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med.* 2015;9(5):358-367.
- Kelly AM, Derr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *MJA.* 2005; 182:24-27.
- Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction.* 2009;104:2067-2074.
- Kleber HD, Weiss RD, Anton RF, et al. for the American Psychiatric Association Workgroup on Substance Use Disorders, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry.* 2006;163(8 Suppl):5-82.
- Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. *J Addict Med.* 2011;5(4):254-263.
- Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. *J Psychopharmacol.* 2017;31(8):1046-1055. doi: 10.1177/0269881117711710.
- Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet.* 2018;391(10118):309-318. doi: 10.1016/S0140-6736(17)32812-X.
- Lexicomp Online. Lexicomp Web site. 2020. <http://online.lexi.com/lco/action/home>. Accessed February 7, 2020.
- Ling W, Wesson D, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry.* 1996;53:401-407.
- Lintzeris N, Leung SY, Dunlop AJ, et al. A randomized controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend.* 2013;131:119-126.
- Lucemyra prescribing information. US WorldMeds, LLC. Louisville, KY. May 2018.
- Ma J, Bao Y, Wang R, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry.* 2019;24(12):1868-1883. doi: 10.1038/s41380-018-0094-5
- Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014;2:CD002207.
- Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend.* 2010;108(1-2):110-114.
- Merlin MA, Saybolt M, Kapitanian R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *Am J Emerg Med.* 2010;28(3):296-303.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2020. Available from: <http://www.micromedexolutions.com/home/dispatch>. Accessed February 7, 2020.
- Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011;(4):CD001333. doi: 10.1002/14651858.CD001333.pub4.
- Naloxone prescribing information. West-Ward Pharmaceuticals. Eatontown, NJ. March 2015.
- Naltrexone tablet prescribing information. SpecGx LLC. Webster Groves, MO. July 2017.

- Narcan Nasal Spray FDA Summary Review. Drugs@FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf. November 18, 2015. Accessed February 7, 2020.
- Narcan nasal spray prescribing information. Adapt Pharma, Inc. Radnor, PA. September 2019.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available at: <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed February 7, 2020.
- Perry AE, Neilson M, Martyn-St James M, et al. Pharmacological interventions for drug-using offenders. *Cochrane Database Syst Rev*. 2015;6:CD010862. doi: 10.1002/14651858.CD010862.pub2.
- Petitjean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend*. 2001;62:97-104.
- Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther*. 1999;66(3):306-314.
- REMS@FDA [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. Available at: <http://www.accessdata.fda.gov/scripts/cder/rems/>. Accessed February 7, 2020.
- Robertson TM, Hendey GW, Stroh G, et al. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care*. 2009;13(4):512-515.
- Sabzghabae AM, Eizadi-Mood N, Yaraghi A, et al. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. *Arch Med Sci*. 2014;10(2):309-314.
- SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 18-4742. Substance Abuse and Mental Health Services Administration Web site. 2018. <https://store.samhsa.gov/system/files/sma18-4742.pdf>. Accessed February 7, 2020.
- SAMHSA. Treatment Improvement Protocol (TIP) 63: Medications for opioid use disorder. June 2019. Available at: https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf. Accessed February 7, 2020.
- Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713-720.
- Schottenfeld RS, Pakes J, O'Connor P, et al. Thrice-weekly vs daily buprenorphine maintenance. *Biol Psychiatry*. 2000;47(12):1072-1079.
- Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol*. 2008;11:641-653.
- Strain E. Pharmacotherapy for opioid use disorder. UpToDate Web site. <https://www.uptodate.com>. Updated January 28, 2020. Accessed February 7, 2020.
- Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther*. 2011;89(3):443-449.
- Sublocade prescribing information. Indivior, Inc. North Chesterfield, VA. October 2019.
- Suboxone film prescribing information. Indivior, Inc. North Chesterfield, VA. October 2019.
- Sullivan MA, Bisaga A, Pavlicova M, et al. A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. *Am J Psychiatry*. 2019;176(2):129-137. doi: 10.1176/appi.ajp.2018.17070732.
- Tanum L, Solli KK, Latif ZE, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry*. 2017;74(12):1197-1205. doi: 10.1001/jamapsychiatry.2017.3206.
- US Department of Health & Human Services (HHS). Naloxone: the opioid reversal drug that saves lives. December 2018. Available at: <https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf>. Accessed February 7, 2020.
- Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2015. Available at: http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp. Accessed February 7, 2020.
- Vivitrol prescribing information. Alkermes, Inc. Waltham, MA. September 2019.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-1246.
- Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008;300(17):2003-2011.
- World Health Organization: Community management of opioid overdose. WHO Web site. 2014. http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/. Accessed February 7, 2020.
- Zubsolv prescribing information. Orexo US, Inc. New York, NY. October 2019.

Publication Date: March 17, 2020